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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/765,026	01/13/1997	MARTINE BARKATS	ST94051-US	5544

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EXAMINER	
GUZO, DAVID	
ART UNIT	PAPER NUMBER
1636	26

DATE MAILED: 12/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/765,026	Applicant(s) BARKATS ET AL.	
	Examiner David Guzo	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47,61-75,78,79,81 and 82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47, 61-75, 78-79, 81 and 82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 47, 61-65, 67, 69-75, 78-79 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenberger et al. in view of Coyle et al. and applicants admissions.

Applicants claim a method of treating diseases such as ALS, Parkinson's disease (PD) hypertension, etc. wherein said diseases are characterized by an excess of free radicals, said method comprising administering to patients a replication defective adenovirus (which can be Ad5 or Ad2, etc.) encoding an intracellular CuZn superoxide dismutase (SOD-1) operably linked to a promoter (which can be the MLP) enabling expression in target cells.

Greenberger et al. (previously cited, see whole document, particularly column 2, lines 4-10; column 8, lines 26-45; column 10, lines 10-22; column 11, lines 40-column 12, lines 1-18, etc.) recites the construction of replication defective recombinant adenoviral vectors (derived from Ad5) which are capable of expressing SOD genes (including SOD-1) wherein the SOD-1 gene is operably linked to a promoter (such as MLP or a promoter appropriate to the target tissue) enabling expression of the SOD in target cells. Greenberger et al. teaches that it is a object of the invention to "...provide a safe and efficient method of transferring oxidation or cation-scavenging protein encoding genes directly into a patient's cells." (Column 2, lines 4-6). Greenberger et al. does not teach the use of the recited adenoviral vectors to treat the specific diseases recited by applicants.

Coyle et al. (previously cited, see whole article, particularly pp. 689-690, 694) recites that the genes encoding SODs are well known, recites the role(s) played by free radicals in diseases such as ALS, PD, etc., reviews the well known roles of the different forms of SODs in reducing the levels of free radicals, the role of increased levels of SOD-1 with protection of brain tissue from ischemic brain damage and the possible correlation between reduction or lose of SOD-1 activity with diseases such as ALS in humans.

Applicants admit, in the instant specification (p.2) that "...it is nowadays recognized that these free radicals are involved in arteriosclerosis, cardiovascular diseases, cirrhosis of the liver, diabetes, cataract formation...Parkinson's disease and cerebral ischemia, in trisomy 21, and...pulmonary hypertension...".

The ordinary skilled artisan, seeking to develop a method for treating diseases which are well known to be associated with excess free radicals, would have been motivated to use the methodologies recited by Greenberger et al. for delivering a SOD gene of interest (in a recombinant adenoviral vector) to a patient for the purpose of scavenging free radicals to treat diseases which Coyle et al. disclose, and applicants admit, are associated with excess free radicals because the ordinary skilled artisan would be using the recombinant adenoviral vectors of Greenberger et al. for their intended purpose (scavenging free radicals in patients). It would have been obvious to the ordinary skilled artisan to use the adenoviral vectors of Greenberger et al. to treat the instantly recited diseases because Greenberger et al. teaches that said vectors can be used to safely and efficiently deliver SOD genes to patients so as to scavenge excess free radicals which Coyle et al. and applicants disclose are well known to be associated with diseases such as ALS, diabetes, etc. Given the teachings of the cited prior art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 66 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenberger et al. in view of Coyle et al., applicants' admissions and Gregory et al.

Greenberger et al., Coyle et al. and applicants' admissions are as cited and applied in the above 103(a) rejection. These references do not teach the generation of adenoviral vectors lacking the E1 and at least one of the E2, E4 or L1-L5 genes.

Gregory et al. (U.S. Patent 5,882,877, issued 3/16/99, effective filing date of 12/3/92, see whole document, particularly column 4 and Claims 1-2, 8-9) teaches the generation of adenoviral vectors lacking the E1 region and at least one of the E2, E4 and L1-L5 genes. Gregory et al. teaches that these vectors are superior to other adenoviral vectors because they can accommodate larger inserts of foreign nucleic acid and contain no potentially harmful adenoviral genes.

The ordinary skilled artisan, seeking to choose an adenoviral vector for delivery to patients for treatment of diseases associated with excess free radicals, would have been motivated to administer recombinant adenoviral vectors encoding SOD-1 (as taught by Greenberger et al.) that do not possess potentially harmful adenoviral genes (as taught by Gregory et al.) for the expected benefit of reducing any adenoviral induced deleterious effects on the patient and allowing larger inserts to be included in the vector. It would have been obvious for the ordinary skilled artisan to do this because the adenoviral vectors disclosed by Gregory et al. are designed to be administered to humans and have all potentially harmful adenoviral genes deleted. Given the teachings of the cited art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be concluded that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Greenberger et al. in view of Coyle et al., applicants' admissions, Le Gal La Salle et al. and Nabel et al.

Greenberger et al., Coyle et al. and applicants' admissions are applied as in the above 103(a) rejection of claims 47, 61-65, 67, 69-75, 78-79 and 81. These references do not teach use the RSV LTR as a promoter to drive expression of a heterologous nucleic acid sequence in an adenoviral vector.

Le Gal La Salle et al. (Previously cited, see whole article, particularly p. 988) recites use of the RSV LTR as a promoter in the context of driving expression of heterologous nucleic acids sequences in an adenoviral vector.

Nabel et al. (U.S. Patent 5,650,306, issued 7/22/97, filed 6/7/93, see whole document, particularly the paragraph bridging columns 3-4) teach that the RSV LTR promoter is a strong promoter commonly used in the art for expression of recombinant DNA molecules.

Greenberger et al., Coyle et al. and applicants' admissions teach the essential aspects of the invention with the exception of using the RSV LTR as the promoter to drive expression of the SOD-1 gene. Greenberger et al. recites that the recombinant adenoviral vector can comprise any active promoter driving expression of the SOD gene (column 10, lines 10-22). One of ordinary skill in the art would have been motivated to use the RSV-LTR promoter because Nabel et al. teaches that the RSV-LTR has been a commonly used strong promoter to drive expression of recombinant DNA molecules and La Gal La Salle et al. teach that the RSV-LTR can be used successfully to drive expression of foreign sequences *in vivo* using recombinant adenoviral vectors. It would have been obvious for the ordinary skilled artisan to incorporate the RSV-LTR promoter into the adenoviral vectors recited by Greenberger et al. for the expected benefit of high

level expression of the foreign gene in target cells. Since the RSV –LTR promoter had also been used successfully to drive expression of heterologous sequences in cells *in vivo* transduced with recombinant adenoviral vectors, the ordinary skilled artisan would have had a reasonable expectation of success in expressing the SOD-1 gene recited in the claims.

Given the new grounds of rejection, applicants' arguments traversing the previous (now withdrawn) rejections are moot.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David Guzo
December 1, 2002

DAVID GUZO
PRIMARY EXAMINER